

**ADVANCES IN TRANSPLANTATION BIOTECHNOLOGY AND ANIMAL TO HUMAN ORGAN
TRANSPLANTS (XENOTRANSPLANTATION)**

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FOREWORD

Over the past decade, the OECD has played a significant role in international and intergovernmental discussions on the policy implications of the development of biotechnology. In the mid-80s, this has included the preparation of a series of reports on scientific principles and concepts relevant to safety assessment and socio-economic and other policy issues.

More recently, the OECD, acknowledging the importance of novel biomedical research in driving forward the applications of new biotechnologies, has expanded its activities in the health-care sector.

The first activities on this sector have included a review of safety and socio-economic issues for two major areas of application: live vaccines and gene therapy. In 1992, the OECD Biotechnology Unit organised a workshop on “Non Target-Effects of Live Vaccines”, followed in 1995 by a workshop on “Gene Delivery Systems” (Ottawa, 1995).

Current projects include a workshop on “Novel Systems for the Study of Human Disease” (Rome, 1996) and a report on “Socio-economic impacts of human health-related biotechnologies”.

Consistent with their interest in leading edge technologies (and their policy implications), and drawing attention to the recent significant biotechnological developments in the field of transplantation, the OECD Member governments through the Working Party on Biotechnology invited the OECD staff to prepare a background paper on the subject of xenotransplantation.

This report, drafted by Dr. Elettra Ronchi, co-ordinator of health projects in the Biotechnology Unit of the OECD, brings together a wide range of material, raising safety, economic and ethical points for consideration by OECD governments.

The preparation of this paper, which precedes the organisation of a workshop to be held in 1997, has included consultations with the UK Department of Health, the World Health Organization (WHO), the US National Institutes of Health, Imutran Ltd. in the United Kingdom, the UK Transplant Support Service Authority, the US Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network (OPTN), the Nuffield Council of Bioethics and the Etablissement Français des Greffes.

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ADVANCES IN TRANSPLANTATION BIOTECHNOLOGY AND ANIMAL TO HUMAN ORGAN TRANSPLANTS (XENOTRANSPLANTATION)

SAFETY, ECONOMIC AND ETHICAL ASPECTS

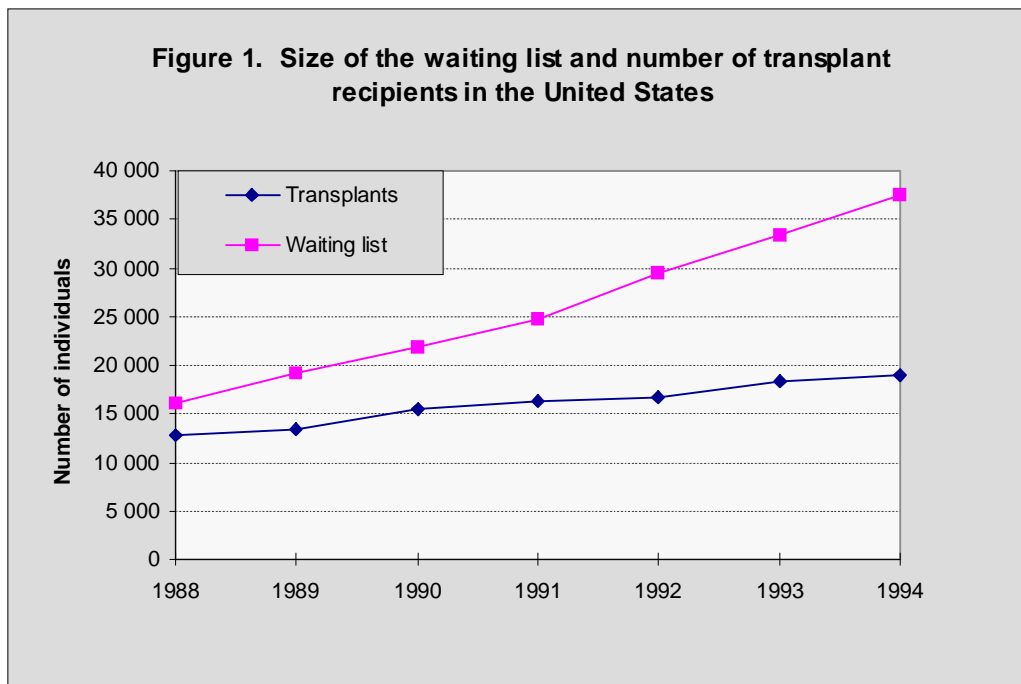
Transplantation in medicine: problems and needs

The first human-to-human organ transplant ever to be reported was carried out in 1954 at the Brigham & Women's Hospital in Boston (United States). However, it was only after the first widely publicised human cardiac allograft procedure performed by Barnard in South Africa (1967) that clinical transplantation witnessed a surge in both enthusiasm and attempted trials. These early trials were marred by numerous failures, as 65 per cent of persons undergoing transplantation before 1970 died within three months of the procedure.

Today, transplantation is considered an accepted practice to treat patients with end-stage organ failure where treatment with drugs or restorative surgery is not feasible. Due to important breakthroughs in tissue typing and immunosuppressant drugs, it is now possible to transplant approximately 25 different organs and tissues, including bone and cartilage, bone marrow, skin, cornea, heart, heart-lung, kidney, liver, lung and pancreas. Furthermore, survival rates have greatly improved. 80 per cent of kidney transplant recipients live for at least one year, and over 60 per cent live for at least five years. Other transplants are not as successful, but even in the least successful cases, more than 50 per cent of recipients live for longer than five years.

A consequence of the successful advances in organ transplantations is that there is an increasing demand for such treatments, and consequently, for human organs. Currently, this demand cannot be adequately met because of the shortage of donors for transplantation.

In the United States alone, the number of transplant recipients (all organs included) increased by 49 per cent between 1988 and 1994 (from 12 786 to 19 017) (Figure 1). The size of the waiting list also increased over the same period (Figure 1). It is apparent that by 1994, the number of transplant recipients in that year was less than half of the patients on the waiting list.

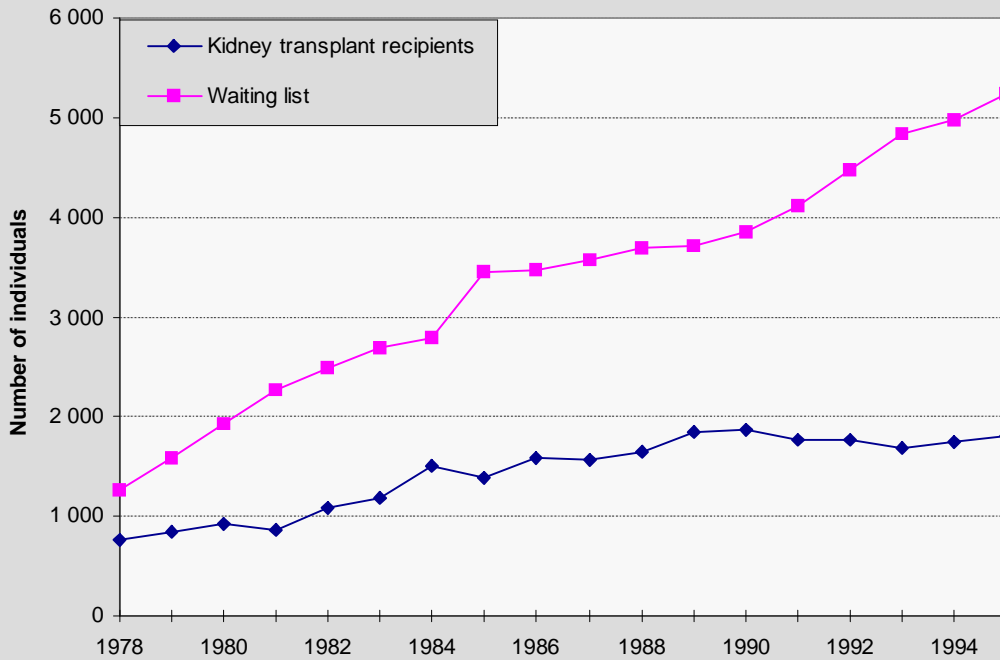


Sources: 1995 Annual Report of the US Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network (OPTN); Transplant Data: 1988-1994. Network for Organ Sharing (UNOS), Richmond, Virginia; Division of Transplantation, Bureau of Health Resources Development, US Department of Health and Human Services, Rockville, Maryland (DOT/HRSA/DHHS).

A similar situation is found in the United Kingdom. This is illustrated in Figure 2, which shows the number of kidney transplants (the most commonly performed transplant operation) and the size of the waiting list between 1978 and 1995 in the United Kingdom and Ireland. In 1978, 765 kidney transplant operations were performed; by 1995, the number of transplants had more than doubled (1 796). During the same period, however, the number of patients on the waiting list increased nearly five-fold, from 1 274 to 5 241.

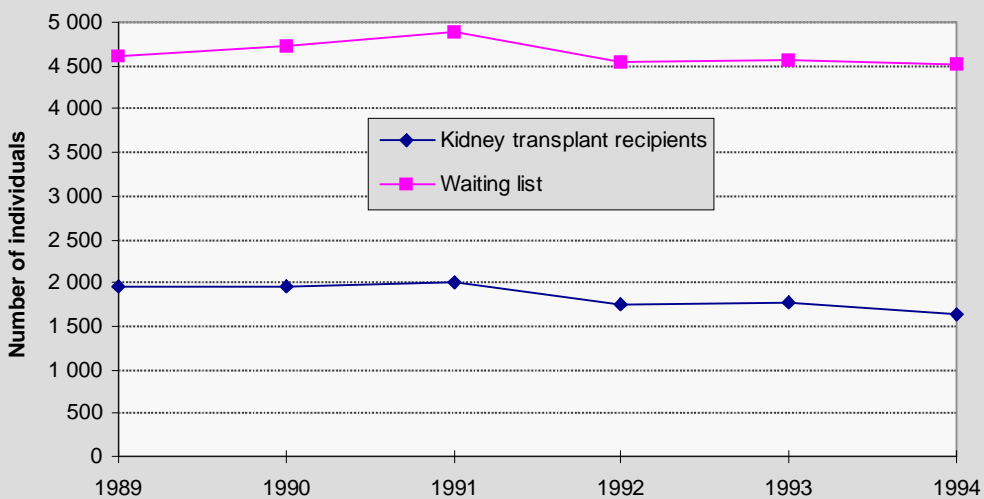
In France¹, the number of kidney transplants performed in 1985 was 1 146. By 1994, despite the steep increase in demand, due to the shortage of donors, only 1 627 kidney transplants could be carried out. It should be noted that France had a donor rate in 1995 of ~14.8 organs per million population (p.m.p.), less than the 19.6 p.m.p. of 1989, and nearly half of that reported by the United States for the same year (~30 organs p.m.p.²). See Figure 3.

Figure 2. Size of the waiting list and number of kidney transplant recipients in the United Kingdom and the Republic of Ireland



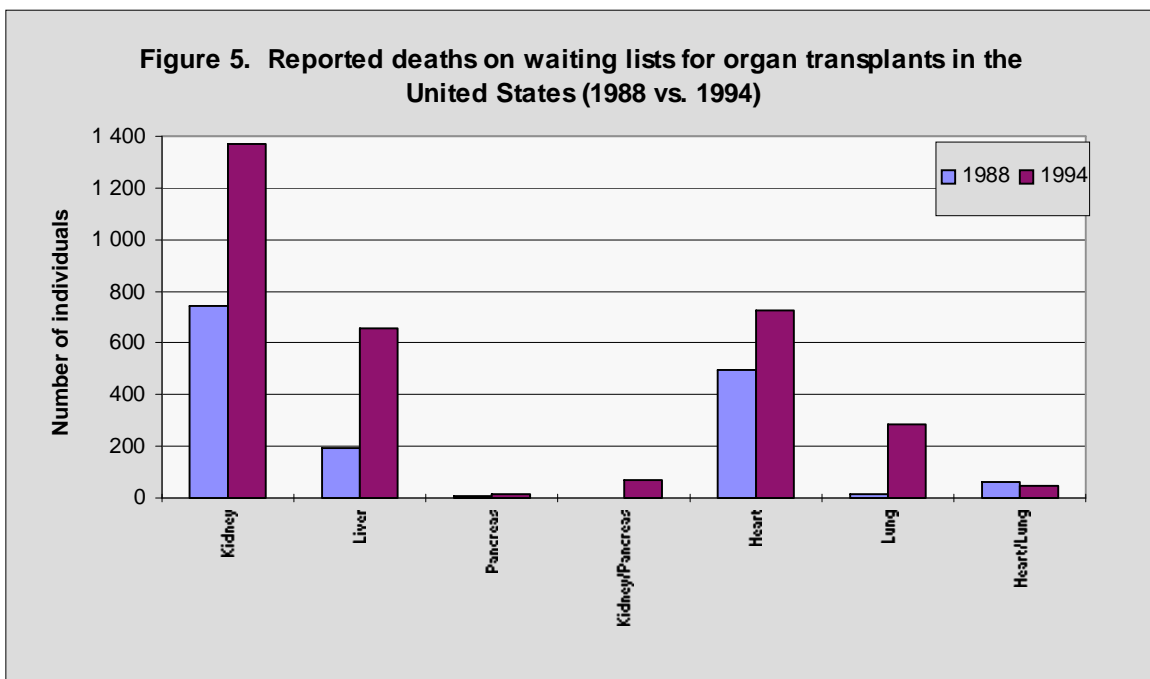
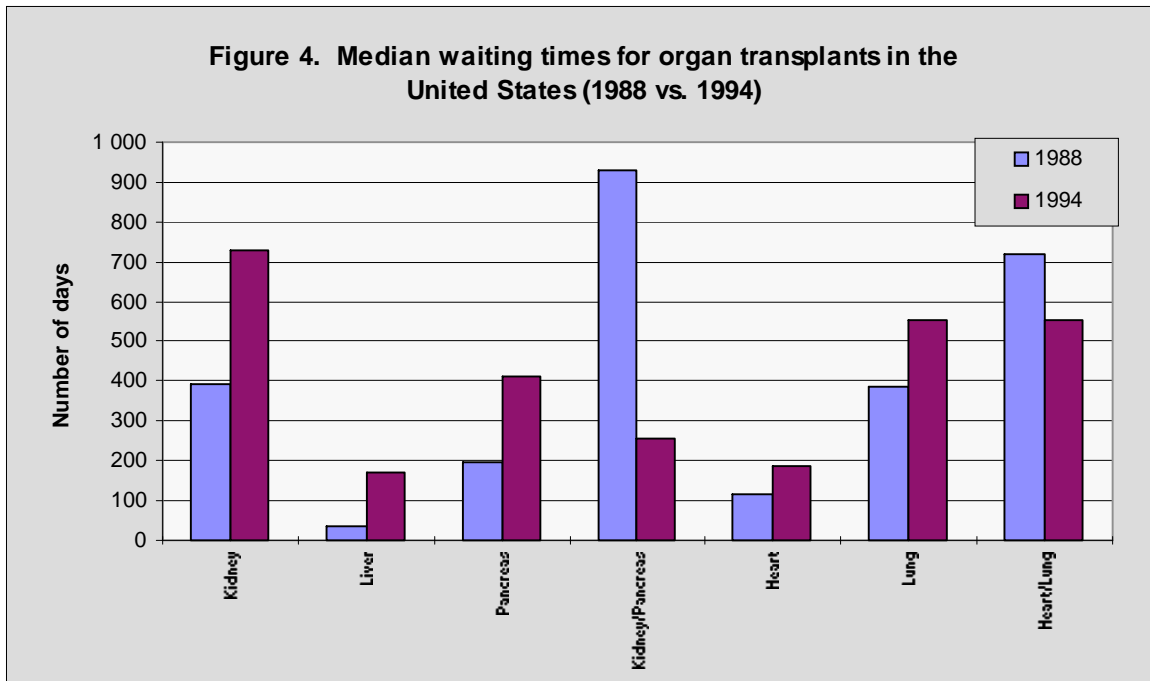
Source: UK Transplant Support Service Authority (UKTSSA) publications and information sheets.

Figure 3. Size of the waiting list and number of kidney transplant recipients in France



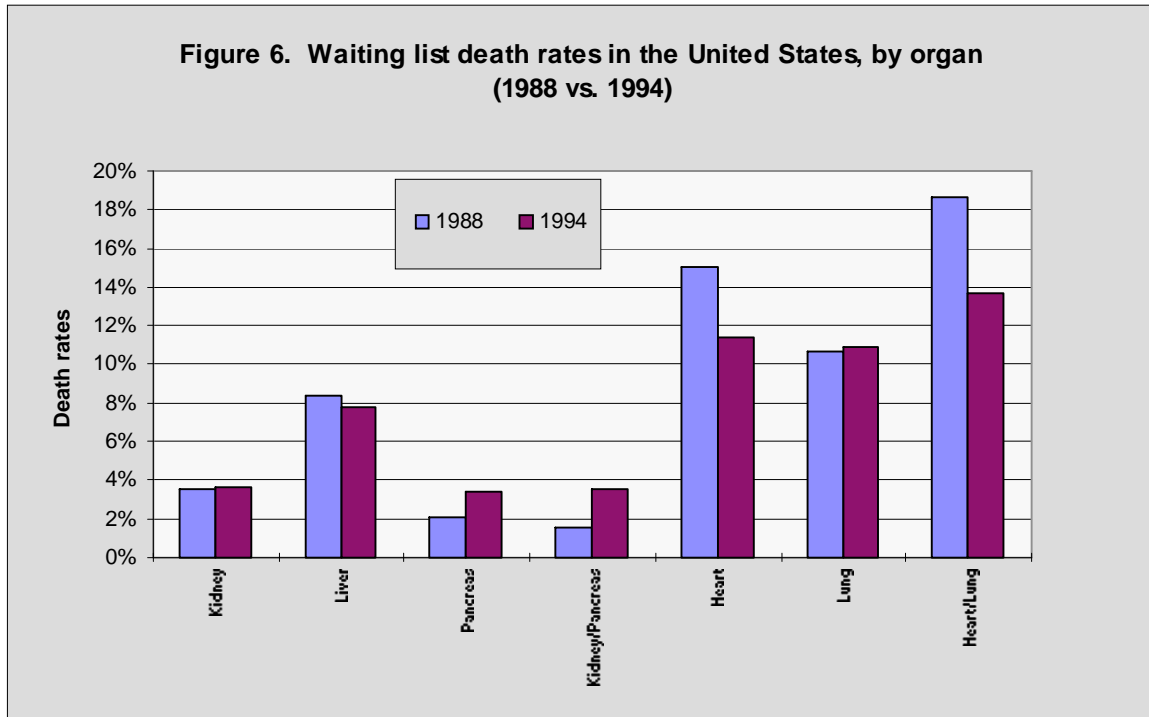
Source: Etablissement français des greffes.

As a consequence of donor organ shortage, the median waiting times for all organs have increased dramatically since the late 1980s. In the United States, the median waiting time for a kidney transplant was nearly two years (728 days) in 1994, compared to one year (394 days) in 1988 (Figure 4). Patients listed for repeat kidney transplants waited twice as long as those listed for their first transplants (e.g. in 1992, second transplant patients waited on average 1 273 days, compared to 558 days for first transplant patients). As a result, the reported deaths on the waiting list in the United States have more than doubled since 1988 (Figure 5). Furthermore, the increasing number of organs transplanted per donor serves to widen the gap between offer and demand.



Source: Network for Organ Sharing (UNOS).

Death rates on the waiting list are highest for heart/lung registrants, followed by heart, lung, and liver registrants (see Figure 6). One likely explanation for the higher death numbers of heart patients is that unlike patients with kidney failure, who can receive dialysis treatment, patients with end-stage heart failure have no alternative form of effective treatment and will die while waiting for a suitable donor.



Source: Network for Organ Sharing (UNOS).

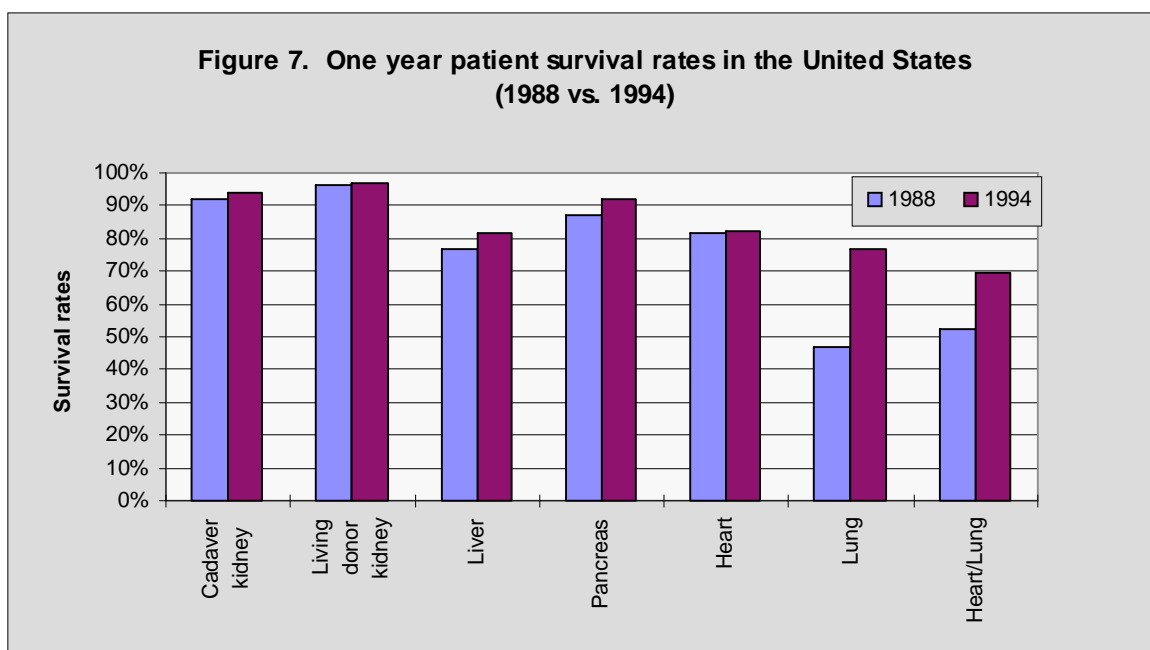
The mechanism of organ rejection

One year graft and patient survival rates are improving every year and for every organ (Figure 7). The greatest relative improvements are seen among heart/lung transplants (as witnessed by the significant decrease in death rates in 1994) (Figure 6).

While one year survival rates improve each year, survival rates for all organ transplants decrease over time (Figure 7, Table 1). The greatest decreases in survival rates are observed in lung transplants, heart/lung transplants and cadaver kidney transplants.

The reason for this decrease in survival rates over time is an ill-understood and progressive process that is thought to be multi-factorial in origin and linked to a phenomenon called chronic rejection.

When a vascularized donor graft is placed in an individual of the same species as the donor (allograft) or in an individual of a different species (xenograft), an immune response is triggered. In the case of allograft transplants, almost half the patients still undergo an acute rejection in the form of a rejection crisis. If the donor organ comes from a different species, the immune response may be immediate (hyperacute rejection), may occur after some days (delayed xenograft rejection), or may occur much later in time (chronic rejection).



Source: Network for Organ Sharing (UNOS).

Table 1. One, two and three year graft and patient survival rates in the United States, by organ (October 1987 - December 1992)

		Number	1 Year Survival		2 Year Survival		3 Year Survival	
			%	Margin of error	%	Margin of error	%	Margin of error
Cadaver donor kidney	Graft survival	38 599	80.3	0.2	74.5	0.2	68.7	0.3
	Patient survival	38 629	93.2	0.1	90.4	0.2	87.5	0.2
Living donor kidney	Graft survival	10 926	91.2	0.3	87.7	0.3	83.7	0.4
	Patient survival	10 931	97.3	0.2	95.9	0.2	94.3	0.3
Liver	Graft survival	12 869	68.0	0.4	63.6	0.4	60.5	0.5
	Patient survival	12 869	78.6	0.4	74.9	0.4	72.2	0.5
Pancreas	Graft survival	2 312	71.9	0.9	66.9	1.0	62.2	1.1
	Patient survival	2 311	89.5	0.6	85.5	0.8	81.7	0.9
Heart	Graft survival	10 131	82.4	0.4	78.3	0.4	74.6	0.5
	Patient survival	10 131	82.4	0.4	78.3	0.4	74.7	0.5
Lung	Graft survival	1 271	68.8	1.3	59.7	1.5	50.8	1.9
	Patient survival	1 271	68.9	1.3	59.7	1.5	50.9	1.9
Heart/Lung	Graft survival	299	59.1	2.9	51.2	3.0	48.1	3.1
	Patient survival	299	59.1	2.9	51.2	3.0	48.1	3.1

Source: Network for Organ Sharing (UNOS).

Acute rejection, frequent in allotransplants, is now fairly well understood. As blood flows through the new organ, the vascular injury associated with transplantation and reperfusion of the graft induces a cascade of complex molecular events that involves the activation of T-cells that produce the cell-mediated response by killing directly foreign cells (cytotoxic T-cells) or by helping other cells in their killing task (helper T-cells), providing soluble biologically-active mediators for other cell types.

Antibodies are molecules that circulate in the blood and bind to foreign molecules (antigens). One important consequence of antibodies binding to antigens is the activation of a complicated reaction called the complement reaction. Complement is a system of more than twenty different blood proteins which, when activated sequentially, attack foreign organisms or cells, and within minutes can destroy them. Nature has endowed the body with a way of distinguishing the “self” from the “non-self” to prevent self-destruction. Thus, the body’s own cells have on their surface complement-regulating proteins which prevent the activation of complement proteins. The most important of these molecules are called decay-accelerating factor (DAF), CD59, and membrane cofactor protein (MCP).

Hyperacute graft rejection is carried out primarily by complement proteins. In the presence of a xenograft, antibodies bind to the xenoantigens present on the endothelial cells (ECs) of blood vessels of the graft. This binding leads to the subsequent activation of complement, intravascular thrombosis and organ failure, which can occur within minutes of transplantation. Acute T-cell mediated rejection, on the other hand, is a somewhat slower process and can occur within days of transplantation and can contribute to delayed xenograft rejection, or may initiate long term chronic rejection.

Unlike hyperacute rejection, chronic rejection is an *ill-understood process*. Its evolution probably consists of four phases:

- i) activation of antibodies since antibody-antigen complexes have been found on the sites of blood vessels;
- ii) intense early T-cell infiltration that declines with time;
- iii) infiltration of macrophages;
- iv) irreversible slow cytotoxic events.

This process may occur over months or years, and leads to irreversible damage to the blood vessels of the transplant.

Both hyperacute and chronic rejection occur in vascularized organs and are strictly linked to the molecular events which follow the reaction of antibodies with the cells that line the blood vessels of the graft, i.e. the endothelial cells (ECs). Thus, the development of an optimal therapeutic regimen that will permit long term function of a graft requires not only inhibition of hyperacute rejection, by blocking xenoreactive antibodies and complement, but also specific interference with other downstream processes related to EC activation.

Unlike solid organs, tissues such as bone marrow do not have major blood vessels passing through them. This means that hyperacute rejection does not usually occur when bone marrow is transplanted. However, in this case, patients may suffer from another ill-understood immune response, graft-versus-host-response which can be fatal; this also because the transplant recipients have to be treated with drugs that suppress or delay the immune response.

A normal individual given bone marrow will mount an immune response against the transplanted cells and destroy them. The immunodeficient or immunosuppressed patient cannot do this and the graft can take and survive. However, the grafted lymphocytes can react against the recipient's own antigen in a graft-versus-host-response. This response, mounted primarily by the T-cells, is the main obstacle to bone marrow transplantation in humans. Multiple methods have been used to deplete T-cells from donor bone marrow to avoid this life-threatening complication. However, T-cell depletion, while decreasing the incidence of graft-versus-host disease, also results in increased failure of engraftment.

Current methods to prevent rejection

There are two main approaches in clinical practice today for preventing graft rejection.

The first is to attempt to closely match the transplanted organ to the recipient's antigens to achieve high histocompatibility between recipient and donor. Donor selection therefore becomes a key issue. It is almost impossible to get a perfect tissue and serological match between individuals (except between identical twins). For live organ donations, usually one of the parents or a close sibling is chosen as donor on the basis of both ABO blood and tissue type combination and anatomical size matching. The goal of tissue typing is to identify the transplantation antigens (HLA) displayed on the cell surface. In the past decade, with the introduction of molecular methodology based on the polymerase chain reaction (PCR), tissue typing has become more accurate, and can be done within the four hours compatible with the time constraints of cadaver organ transplantation.

The second approach to prevent graft rejection is to suppress the patient's immune system with immunosuppressive drugs. In 1981, the first randomised clinical trials were initiated in Europe and Canada for what is now considered the best immunosuppressive agent on the market, cyclosporine A. Cyclosporine A, which acts by inhibiting T-cell activity, in combination with steroids, has established a very high benchmark of success in suppressing hyperacute rejection. However, the principal limiting effect of this drug is its dose-related nephrotoxicity. Therefore, in the past few years there has been a renewed interest in developing immunosuppressive agents to replace cyclosporine A in combination protocols.

Infections in organ transplant recipients on immunosuppressive treatment

The major drawback in using immunosuppressive agents is that the patient's immune system not only tolerates the transplanted organ, but also becomes more susceptible toward life-threatening infections and certain types of cancer. No other patient has a greater depth of immune compromise than the bone-marrow transplant recipient. Many of these patients are hyposplenic or have had the spleen, the principal organ for antibody response, removed. Thus, specific antibody responses are impaired in these patients, who become highly susceptible to opportunistic infections.

A recent US multi-centre liver study group (New England Journal of Medicine, 1994) reported the results of a randomised trial comparing different immunosuppressants with liver transplants. Independently of the type of drug used, major infections occurred in 39 per cent of patients (0.68 episodes per patient) within one year following transplantation.

Hepatitis-C virus (HCV) has recently emerged as a leading cause of liver disease in solid-organ transplant recipients. In the United States, 63 per cent of renal transplant centres do not use kidneys from

anti-HCV-positive donors (Schweitzer *et al.*, 1993). However, since most anti-HCV tests to date have low specificity (in general, though, toward false positives), HCV remains a concern.

Hepatitis-B virus (HBV) recurrence is the second leading cause of graft failure. Factors leading to recurrence after liver transplant are poorly understood. Retransplantation for HBV recurrence has very poor prognosis and is not presently indicated because of high mortality (5 per cent survival rate after one year). Interferon as either therapy or to prevent recurrence after transplantation has not been efficacious.

Cytomegalovirus and Epstein-Barr virus infection are other common complications associated with transplantation. Viral infections may also play a role in causing many post-transplant neoplasms, including non-Hodgkin's lymphomas, skin cancers, Kaposi's sarcoma, carcinomas, hepatomas and leiomyosarcomas. Interestingly, cessation of immunosuppressive therapy, as the only treatment, can produce 20-38 per cent of complete remission of, e.g. Kaposi's sarcoma and non-Hodgkin's lymphomas.

Finally, invasive fungal infections, particularly aspergillosis, remain one of the most challenging opportunistic infections in many patients after transplantation.

In conclusion, once transplanted, graft maintenance requires lifelong non-specific immunosuppression to prevent the recipient's immune system from rejecting the donor organ. The use of immunosuppressive substances is associated with an increased rate of malignancy and opportunistic infections. Moreover, chronic rejection occurs in spite of the use of these agents, and remains the primary cause of graft failure.

Chimaerisms and tolerance

Once an organ is transplanted successfully, its tissues will start an active cellular and molecular exchange with the recipient's cells and organs. Some donor cells will migrate out of the graft into the host's lymphoid (tissues of the immune system) and nonlymphoid tissues. This "two-way" traffic was first observed in stable liver recipients by Dr. Starzl in 1992 at the University of Pittsburgh Transplantation Institute. These patients were capable of retaining excellent function of the transplanted liver without immunosuppressive treatment. The reason was, without exception, they had become microchimaeric, i.e. donor cells (leukocytes), had migrated from the graft to become widely disseminated in their extrahepatic tissues (Starzl *et al.*, 1992; Starzl *et al.*, 1993a). Similar observations in a small proportion of kidney graft recipients have led to the hypothesis that the establishment of microchimaerism is a necessary condition for the successful outcome of all organ grafts and of tolerance to antigens present in the donor organ. Following this principle, bone marrow from a different, but closely related species could be transplanted to induce microchimaerism and donor-specific tolerance to subsequent grafts from the same source. Donor-specific tolerance would eliminate the need and hazards of lifelong immunosuppression for transplant patients. However, this approach involves some complicated procedures, and has still some potentially life-threatening consequences due to graft-versus-host disease. First, the recipient's immune system has to be transiently ablated before and during donor bone marrow transplant. Second, donor haematopoietic elements have to repopulate the recipients' bone marrow in the presence of the host's own cells. There are several difficulties in this procedure and current research is focused on methods to achieve chimaerism without having to subject the host to transient bone marrow ablation and to T-cell depletion of donor marrow to avoid graft-versus-host disease. Nonetheless, the application of allogeneic and/or xenogeneic chimaerism could dramatically expand the donor pool available to numerous patients who might otherwise never survive to transplantation.

Xenotransplantation

Clinical cross-species transplantation or xenotransplantation dates back to the early twentieth century, with kidney xenografts from rabbits, pigs, goats, lambs and non-human primate donors. However, this practice was soon abandoned because of the massive and rapid death of the transplanted organs after xenografting.

In 1963, with six chimpanzee-to-human kidney transplants, Reemtsma and colleagues (Reemtsma *et al.*, 1964) in the United States started a new wave of attempts at xenotransplantation. Most of the patients died within days. In 1964, Hardy and colleagues at the University of Mississippi (Hardy *et al.*, 1964) performed the first cardiac xenotransplantation which was soon followed by eight other attempts by other groups. Five of the donors for these attempts were non-human primates (two baboons and three chimpanzees), and three were farm animals (one sheep, two pigs). The longest survivor (20 days) of the patients in this series was a new-born infant who made headlines news as “Baby Fae” in 1984 (Bailey *et al.*, 1984).

Eventually, attempts at xenotransplantation became rare because of the unacceptable early mortality due to hyperacute organ rejection.

More recently, the introduction of immunosuppressive regimens and advances in the knowledge of the immune system have rekindled interest in this procedure. During the past three years, investigators at the University of Pittsburgh reported two cases in which they transplanted a baboon liver into a human recipient, obtaining a 70-day survival in their first reported case, and a 26-day survival in the second (Starzl *et al.*, 1993*b*). More recently, Czaplicki and colleagues in 1992 described a case in which they attempted a pig-to-human heart xenotransplantation. The patient survived less than 24 hours; interestingly, though, not because of hyperacute rejection. Their protocol included an unusual immunosuppressive regimen and extracorporeal perfusion of the pig’s heart with the recipient's blood in an attempt to remove human anti-pig antibodies.

In the past three years, a number of other approaches for preventing or reducing hyperacute rejection have been developed. Several of these (described further below) hold great promise and will warrant advancement in clinical and surgical practice. Therefore, the question for many researchers today seems to be, not how, but *when*, xenotransplantation should advance to the clinical arena.

Dramatic prolongation of xenograft survival through experiments in rodent and non-human primate models having been demonstrated, it remains to be established which model most closely approximates the human condition. The answer to this question seems obvious to many. The United Kingdom-based company, Imutran Ltd., has announced its intention to start trials transplanting pig organs into human patients in 1996 (Nature Medicine, 1995). Xenotransplantation of pig foetal neural tissue in patients affected by Parkinson’s disease is currently taking place in the United States. Furthermore, the first baboon bone marrow transplant for treating an AIDS patient was carried out (albeit unsuccessfully) in the United States in December 1995.

It appears to be the opinion of many that the limitations of precisely predicting the applicability of laboratory evidence to humans are now insurmountable and that answers should be sought directly from experiments in humans. However, several questions remain unanswered.

- Under what conditions should the experimentation proceed, and what is the minimal goal of the clinical applications of xenotransplantation?

- Are we applying premature use of unproven procedures in fellow humans?
- Is xenotransplantation going to provide primarily “a bridge”, i.e. a temporary method of life support designed to carry a patient until a human organ can be found, or is it going to replace allotransplantation?

Clearly, the use of xenografts solely as bridges will not increase the donor pool and resolve the problem of organ shortage. Therefore, successful permanent xenotransplantation seems to be the target of most international research efforts. Is this an acceptable and reasonable target?

Pigs as organ donors

Pig tissues seem to be most appropriate for xenotransplantation because this species shares many biological features with humans (Cooper *et al.*, 1991). Of potential use could be the kidney and heart, whereas the liver, as a major protein-producing organ, may pose additional problems. In addition, there is a need for isolated pancreatic islet cells for transplantation to diabetic patients. The major problem with xenografts of pig origin is that if a pig organ is transplanted into a human being, hyperacute rejection is extremely strong and is followed by destruction of the graft within minutes.

Several groups have now demonstrated (Sandrin *et al.*, 1993) that the major target of human anti-pig immune reaction is a carbohydrate terminal sugar Gal α on the endothelial walls of the blood vessels of the transplanted pig organ. However, not all pig organs are rich in this highly immunogenic molecule. The islet cells and exocrine tissues of the pig pancreas seem to have less Gal α , and although human anti-pig antibodies bind to islet cells, they fail to kill them.

Therefore, a number of clinical trials are already in progress examining transplanted pig islets in insulin-dependent diabetic kidney transplant patients (Groth *et al.*, 1993). Recently, in Sweden, ten diabetic patients received pig foetal islet cells and in four of these patients, pig cells survived for up to 14 months. Thus, preliminary results seem to indicate that porcine foetal islet cells can be safely transplanted into diabetic patients, intraportally or under the kidney capsule, provided that the amount of transplanted tissue is not excessive. After transplantation, the porcine cells can survive for several months and seem to be functional, even if the amounts of insulin produced are below the normal level (~20 per cent of the level of a healthy individual) (Groth *et al.*, 1994).

However, today's major efforts are toward the resolution of heart, liver and kidney organ shortage and the final target of most research is, in the words of Dr. Bollinger of Duke University Medical Center (Durham, North Carolina), “a properly engineered transgenic pig with low expression of target antigens, enhanced ability to regulate the action of human complement, recognition functions required to generate a *de novo* immune response, few human pathogens, and ready availability”.

How is this currently being pursued?

As shown above, there are three phases of rejection of a discordant vascularized xenograft: hyperacute and delayed xenograft rejection (HAR and DXR, respectively) followed by T-cell mediated chronic rejection. This process is viewed by many as a continuum.

The key role played by complement in inducing HAR, as explained above, has been demonstrated by both *in vitro* and *in vivo* studies (Kemp *et al.*, 1982).

The complement cascade is regulated by specific proteins such as DAF, MCP and CD59 (known as regulators of complement activation, RCAs) that are species specific. In 1991, Atkinson and colleagues (Atkinson *et al.*, 1991) hypothesised that expression of these proteins by pig organs would down-regulate the activation of human complement and could prevent HAR. *In vitro* experiments demonstrated that this was true (Damasso *et al.*, 1991). In the light of these results, the production of mice and pigs genetically-engineered to express human RCAs has been undertaken by many research groups around the world (Cary *et al.*, 1993; Cozzi and White, 1995). The idea is that when an organ from a modified pig is transplanted into a human being, the RCA proteins on the cells of the pig organ will inhibit the activation of complement and consequently prevent HAR.

However, many difficulties are still to be overcome; for example, which RCA proteins or combination of RCAs to use remains unclear. Furthermore, would total inhibition of complement and blocking of xenoantibodies action solve the xenograft rejection problem?

A slightly different approach, pursued by other groups, is to modify pigs so that they no longer have the antigens that are known to be the major target of human antibodies, i.e. the carbohydrate Gal α (see above). Since genes cannot be deleted from pigs at the moment, (suitable pig embryonic stem cells are not yet available) this involves making transgenic pigs containing a human gene which has the effect of reducing the levels of the Gal α antigen.

The general hope is that by blocking HAR and EC activation, the manifestations of delayed xenograft rejection will be “milder”, resulting in the prevention of rejection altogether.

Provided that a combination of these new approaches and known immunosuppressive treatments can successfully defeat rejection, other clinical challenges remain to be solved:

- Will pig organs be physiologically capable of supporting prolonged human life?
- What precautions should be taken to avoid the transfer of porcine pathogens to the immunosuppressed human recipient?

Indeed, the risk of transferring micro-organisms from an animal to a patient is still a major concern when performing pig-to-man transplants. One way to reduce this hazard would be to use donor pigs bred under specific pathogen-free conditions. Nevertheless, even seemingly healthy animals may carry zoonotic infections.

A number of studies have reviewed the micro-organisms that pigs may harbour and transmit to humans (Bachman, 1989; Bjoersdorff *et al.*, 1992). Several bacteria and fungi are common to sows and may remain viable in the interstitial tissues, and in culture media, even in pigs reared in controlled conditions. Among these are *Toxoplasma gondii*, *Leptospira interrogans*, and *Aspergillus fumigatus*.

Furthermore, some of the porcine viral infections are zoonotic and various virus species are related to species affecting humans, e.g. the swine influenza virus. Therefore, if porcine tissue is to be transplanted into humans, guidelines for stringent microbiological screening programmes must be developed.

Baboons as organ donors

Present experiments on African green (vervet) monkey-to-baboon liver transplants (Mieles *et al.*, 1995) would suggest that the pharmacological immunosuppressive agents that are currently available could enable a baboon organ to function in a human for a period of at least days or weeks. Furthermore, there seems to be considerable overlap between baboon and human metabolic functions (Luo *et al.*, 1995). Thus, the baboon has been identified as an animal that can supply organs on a smaller scale than the pig, but has better immunological compatibility with humans. Thus, the baboon organ could be utilised as a bridge to maintain human life until a human organ became available.

The heart and liver are the two organs most likely to be used since there is no real need to bridge kidneys in view of the availability of dialysis. On the other hand, the baboon heart is too small for use in adult humans and would primarily be utilised in infants and small children. However, the most pressing concern with this source of xenografts is the inherent high risk of transmitting viruses to humans.

Since the very beginning of xenotransplantation, there have been a few reports that have addressed this issue. In 1987, a study from Cape Town (South Africa) (Van der Riet *et al.*, 1987) investigated 20 different viruses in wild-caught baboons, wild-caught African green monkeys and captive-bred African green monkeys. Baboons were found positive for Herpes simplex virus 1 (HSV-1), varicella zoster, two strains of rotaviruses (SA6 and SA11) and human cytomegalovirus (CMV). African green monkeys were found to be positive for more infectious agents than baboons, but monkeys bred in captivity under controlled conditions exhibited a lower rate of viral infections. The authors of the study recommended precluding the use of baboons in xenotransplantation unless they could be shown to be free of at least those infectious agents known to pose a serious threat to human health, e.g. *Mycobacterium tuberculosis*, herpes viruses, exogenous retroviruses, and Marburg virus.

A report from France in 1993 (Chiche *et al.*, 1993) documented the results of screening 30 baboons as potential organ donors. Eight of these baboons were found to be suitable as donors. The majority were excluded on the basis of positive serology to infectious agents, size, age and anatomical problems.

A study of 31 adult male baboons in Pittsburgh in 1994 concluded that 52 per cent of the animals were inadequate as donors in view of positive results with regard to retroviruses and toxoplasma (Michels *et al.*, 1994).

Recently, a study in the United States (Luo *et al.*, 1995) on ten adult baboons reported a high incidence of foamyvirus and DNA viruses (SA8, SA6, HSV, CMV and EBV), but this was not thought to exclude them as organ donors. Hepatitis-A serology was positive in four baboons, but hepatitis-B and C were negative in all. In conclusion, on the basis of a series of tests for known micro-organisms, six, or possibly seven, of these baboons were found acceptable as organ donors.

However, the authors of this study also acknowledged the need for further studies; particularly in regard to the presence of endogenous type-C and -D retroviruses that have the potential to become oncogenic. Furthermore, it is now well-established that baboons in the wild can become infected with Simian Immunodeficiency Virus (SIV) (Jin *et al.*, 1994) which is similar to the virus that causes AIDS, and the presence of this virus should be tested directly from lymphocyte extracts.

Clearly, the behaviour of any of these viruses in the immunocompromised host remains unknown. Further practical considerations which are likely to constrain the use of baboons as organ donors are that baboons:

- have mainly one offspring per year;
- have a long pregnancy; and that
- no transgenics are readily available.

Therefore, xenotransplantation involving donor baboons is still very controversial and current national guidelines from various OECD countries seem to reflect this controversy and difference of opinions.

An additional important issue linked to the potential use of primates as organ donors is that the very reason which makes primates well-suited for transplantation, i.e. their close evolutionary relatedness to humans, creates concerns over the ethics of this practice.

Currently in the United Kingdom, as in many other OECD countries, the use of primates is strictly controlled with only very small numbers being used for research purposes. Thus, to breed primates on a large scale for organ donation would be contrary to the currently accepted guidelines in various countries. Therefore, the ethical issues raised by the use of primates for xenotransplantation require further detailed exploration.

Current national and international draft guidelines on xenotransplantation

In response to international concerns about the possible transfer of infectious diseases in the population through transplantation, the World Health Organization has established a WHO Task Force on Organ Transplantation whose mandate was defined by the Advisory Committee on Health Research (ACHR) in October 1995. Among other objectives, the Task Force is to promote studies and resolutions on the full range of issues raised by expanding technologies to recover and transplant organs.

The next meeting of the Task Force of the ACHR should review a number of issues including xenotransplantation.

The office of Zoonoses Prevention and Control, Division of Emerging and other Communicable Diseases Surveillance and Control has developed the first draft of a WHO guideline on xenotransplants and the prevention of xenozoonoses.

These guidelines deal with the assessment of the risk of transmission of contagious diseases from animal tissues to human recipients considering known, as well as unknown, agents. These guidelines will not address other issues related to xenotransplantation such as ethics, animal welfare, socio-economics and technical flexibility. The draft has been reviewed by a number of specialists and a second draft should become available soon. WHO plans to hold an expert meeting for the final review and endorsement of the guidelines by the fall of 1996.

Guidelines addressing the issue of infectious agents that may be associated with xenotransplantation are also being developed in the United States (by Public Health Working Groups at the Food and Drug Administration and the National Institutes of Health). Publication of these guidelines is expected for summer of 1996.

In the United Kingdom a Working Party on Xenografts was set up in 1995 by the Nuffield Council on Bioethics. This group has recently released a report that reviews the progress made in developing xenotransplantation as a procedure and addresses a range of key questions:

- What effective alternatives exist?
- Is it ethically acceptable to use animals for this purpose -- specifically primates and transgenic pigs?
- Will xenografts be safe?
- How will patients react?

A summary of the recommendations from this body are attached to this report, as an annex.

The UK government has set up an Advisory Group on the Ethics of Xenotransplantation to review the acceptability of xenotransplantation and the ethical framework within which it may be undertaken. The group is due to report to Ministers this summer. Also in the United Kingdom, the Advisory Committee on Dangerous Pathogens is considering the risk of infectious disease and xenotransplantation, and with the above Advisory Group, co-hosted a workshop entitled "Infectious Disease and Xenotransplantation" in April, 1996 in London.

Economic aspects

A number of biotechnology companies are developing new approaches to effective xenotransplantation.

T-Cell Sciences Inc., a publicly traded biotechnology company in Massachusetts is working on an injectable complement inhibitor, a substance the company calls sCR1 or soluble complement receptor type 1. The company has been granted a patent for the preparation of this product for therapeutic use together with the Johns Hopkins University (Baltimore, Maryland) and the Brigham and Women's Hospital (Boston, Massachusetts).

BioTransplant Inc., a privately held company in Charlestown, Massachusetts, and Cell Genesys Inc. (Foster City, California) are working on tolerance and chimaerism with the support of Sandoz Pharma AG (Basel, Switzerland), and Massachusetts General Hospital (Boston). Cell Genesys was granted a patent in 1995 on a procedure involving homologous recombination for universal donor cells and chimaeric mammalian hosts.

Genpharm International, a California-based biotechnology company has developed a transgenic immunodeficient mouse depleted in mature T-cells, making it useful for several studies in the field. The company was granted the second animal patent ever issued in the United States. The first went to Harvard University in 1988 for the Oncomouse, a rodent genetically created to grow malignant tumours for cancer research.

Alexion Pharmaceuticals Inc., a privately held biotechnology company in New Haven, Connecticut uses a combined transgenics and anti-rejection biochemistry approach to xenotransplantation. Researchers at Alexion have created a dual-acting fusion gene that incorporates the functional domains of two genes coding for the complement inhibitors DAF and CD59. With this fusion gene they hope to create transgenic pigs. At the same time, they hope to incorporate a third gene, the H-transferase gene, that will counter the actions of the highly immunogenic Gal α epitope.

Nextran Corp. in Princeton, New Jersey, a subsidiary of Baxter Healthcare Corp., (Deerfield, Illinois) is using pro-nuclear micro-injection to create transgenic pigs incorporating human genes that code for complement inhibitory proteins. Pro-nuclear micro-injection is a proprietary transgenic technology exclusively licensed from Princeton, New Jersey-based DNX Corp., until recently a co-owner of Nextran.

Imutran Ltd., a biotechnology company in Cambridge, England, owned by Sandoz Pharma AG of Basel (Switzerland) has also developed transgenic pigs that incorporate the genes for the complement inhibitory proteins DAF, MCP and CD59. This work is done in collaboration with the University of Cambridge. The company has applied for several patents and should soon be granted a European and a US patent on its technology. However, the company has to cope with the current uncertainties in regard to article 53(b) of the European Patent Convention, which may limit the patentability of genetically modified animals.

In addition to the above biotechnology companies, in 1995 the European Society for Organ Transplantation (ESOT) identified, through a survey, eleven enterprises who were developing new immunosuppressive substances/antibodies (Table 2). The underlying reason for this inquiry by ESOT was the concern about the rapidly proliferating development of new immunosuppressive agents and the growing difficulty for the members of ESOT and the medical community to remain informed.

Table 2. New immunosuppressive compounds

Name	Producer	Description
anti-CD4 mAb (SB 210396)	SmithKline Beecham Pharmaceuticals	Humanised primate mAb to the lymphocyte surface antigen CD4
Antilfa (Oculimomab)	Pasteur-Mérieux IMTIX	Anti-LFA-1 α subunit (CD 11a); mouse IgG1
ATG-S-Fresenius S (new modified)	Fresenius AG	Polyclonal rabbit Ab against T lymphocytes
BTI-322	Bio Transplant Inc	Anti-CD2 monoclonal antibody
Simulect (CHI 621)	Sandoz Pharma AG	Chimaeric mouse/human monoclonal antibody with specificity for IL-2R (CD25)
Enlimomab	Boehringer Ingelheim AG	Monoclonal antibody, murine IgG ₁
Leukotac (BT563)	Biotest Pharma GmbH	Mouse monoclonal IgG1 anti-human IL-2 receptor (α -chain) antibody
Monoclonal rat-AB-cocktail	Fresenius AG	Anti-CD5 and anti-CD7
Zenapax, HAT (Daclixi mab)	Hoffmann-La Roche	Recombinant monoclonal immunoglobulin of the human IgG1 isotype
Azaspirane SKF 106615 (MTAC)	SmithKline Beecham Pharmaceuticals	Azaspirane/macrophage targeting anti-arthritic compound (MTAC)
CellCept (mycophenolate mofetil)	Hoffmann-La Roche	Antimetabolite
Leflunomide	Hoechst AG	
Prograf/Tacrolimus/FK506	Fujisawa GmbH	Macrolide lactone with potent <i>in vitro</i> and <i>in vivo</i> immunosuppressive activity
SDZRAD	Sandoz Pharma AG	Macrolide of the rapamycin class
Sandimmun Neoral	Sandoz Pharma AG	New formulation, microemulsion, of Sandimmun ^R
Sirolimus (rapamycin)	Wyeth-Ayerst	Macrolide antibiotic isolated from <i>Streptomyces hygroscopicus</i>

Source: ESOT, 1995.

Clearly, the field has attracted, and is attracting, significant private investment. The market is estimated at 100 000 patients per year. Thus, the obvious questions: What will then be the cost of xenotransplantation compared with human organ transplantation, and will it be cost-effective?

The costs of present transplantation procedures were addressed in several studies at the end of the 1980s, in particular in regard to kidney transplantation.

The direct costs of peritoneal dialysis per patient in France is about FF 140 000 per year (similarly in the United Kingdom, where the cost is about £18 000 per year), somewhat more expensive if carried out in the hospital or at home (Lacronique, 1989). In France, in 1987, nearly 15 000 patients underwent dialysis. Thus, considering all forms of dialysis, the total cost in France in 1987 for renal dialysis was about FF 4.7 billion.

In contrast, according to a study by INSERM (France), the average cost of a kidney transplant for the first year of survival after surgery (including immunosuppressive drugs and all other follow-up treatments) is FF 170 000. For the second year, the cost is estimated to drop to FF 47 200, for the third year to rise to FF 52 250. These costs include the maintenance of an immunosuppressive regime with cyclosporine A that can amount to FF 20 000-30 000 per year (about £3 000-5 000 in the United Kingdom).

Thus, all considered, in the long term, transplantation is estimated to produce a savings of 63 per cent over total medical expenses for a renal patient when compared to life-long dialysis treatment.

The cost of other transplant operations varies according to how long the patient is hospitalised. In France, a liver transplant costs on average FF 280 000 (£15 000 in the United Kingdom), while heart transplants are of the order of FF 192 000 (£10 000-18 000 in the United Kingdom). The cost-benefit analysis in these cases has to take into account the fact that without transplantation the patient would have no chance of surviving. Thus, the most important savings is in indirect costs, i.e. the quality of life, and most importantly, the “life-years” gained by these terminal patients.

Xenotransplantation will most likely not lead to a reduction in these average costs. The costs of the operation will be the same, except that the organs will have to be purchased. The cost of an organ from a transgenic pig is likely to be high in the next few years, reflecting the cost of the innovation required to produce it as well as the breeding and rearing of the animals in controlled conditions. If the development of transgenic animals will result in animal organs and tissues that are less immunogenic, then one could envision a savings in immunosuppressants. However, there would still be the new charge of monitoring xenograft recipients for evidence of diseases.

The use of organs as “bridging devices” will most likely increase the overall direct costs of transplantation, and may be, in the long term, much less cost-effective.

Conclusions

The issues examined in this report are of global concern and they should be addressed in international fora. Implicit in this statement is the notion that xenotransplantation may become a feasible surgical procedure in the near future. One of the most pressing concerns will then be the safety of the use of primate or porcine organs and tissues for xenotransplantation.

Current national guidelines from various OECD countries unanimously suggest a cautious attitude toward xenotransplantation, in particular where primates are involved. However, there is no clear consensus on the extent to which use of primates or pigs may or should be allowed. A risk associated with the transplantation of baboon organs into human beings is the possible transfer of new viruses into the human population. There is no doubt that screening donor animals for known zoonoses or animal viruses will decrease this possibility. However, there seems to be little knowledge on how to quantify the risk linked to unknown viruses or zoonoses which may go unobserved through standard screening procedures.

The recent outbreak of Ebola virus in Africa, of hantavirus in the United States, and the re-emergence of dengue fever are reminders that emerging diseases are global issues and that guidelines on medical and research practices on xenotransplantation should be harmonized.

The World Health Organization is ideally placed to co-ordinate such an effort.

However, the re-emergence of xenotransplantation has also raised ethical and socio-economic issues that would best be addressed by organisations such as UNESCO and the OECD. Animal rights advocates question the science and ethics of the exploitation of non-human species while other critics fear that the rush to commercialise xenotransplantation may preclude a full exploration of the impact on health care systems and the possible alternatives to the procedure. Could better health education and prevention lead to less demand for hearts and other organs? Could artificial organs soon meet the same requirements? Could different legislation on the consent requirement increase human organ donation?

Another issue is that most research in the field is currently carried out by a half-dozen biotechnology companies who will wish to patent the organs and tissues that result from their research and investment efforts. There has been much discussion on whether or not patenting transgenic animals is ethical and whether or not it is legal under current patent laws.

In Europe, the European Commission is trying to clarify the situation with a proposed directive that would clarify the patentability of genetically-altered animals and plants. An earlier version of the proposal was hotly debated, and finally rejected (March 1995) by the European Parliament. The consequences of international differences in intellectual property right legislation in this particular field may lead to difficulties for co-operation on research, investments and diffusion of the new medical technology.

Since human clinical trials are likely to occur very soon in several countries, international co-operation should ensure that adequate guidelines are promptly in place to enable effective review of clinical evidence and to prevent possible public health hazards, at the same time allowing medical progress and equitable technology transfer.

NOTES

1. Source: France Transplant.
2. Source: UNOS and WHO population indicators.

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ANNEX

WORKING PARTY ON XENOGRAFTS (OF THE NUFFIELD COUNCIL ON BIOETHICS)

SUMMARY OF RECOMMENDATIONS

Xenotransplantation raises a particularly wide range of concerns about which people have differing and strongly held views. The Working Party has concluded that the development of xenotransplantation should continue subject to rigorous regulation to ensure protection for potential human recipients and care for animal welfare. The recommendations of the Working Party are as follows:

Animal concerns: principles

- 1 The Working Party endorses the special protection afforded to primates used for medical and scientific purposes. Non-primate species should be regarded as the source animals of choice for xenotransplantation.
- 2 The use of pigs for the routine supply of organs for xenotransplantation is ethically acceptable. The use of transgenic pigs that have been genetically modified to reduce the human immune response to pig organs is also ethically acceptable.

Animal concerns: practice

- 3 The Home Office should require that all animals used for xenotransplantation are protected under the Animals (Scientific Procedures) Act 1986. Thus, the standards set by the 1986 Act should become the minimum for the industry. The convention by which the Animal Procedures Committee advises on project licenses in difficult areas should extend to applications for the use of animals for xenotransplantation.
- 4 When decisions are made about the acceptability of using animals for xenotransplantation, particular attention should be paid to reducing the adverse effect associated with the need to produce animals free from infectious organisms. The Animals (Scientific Procedures) Act should continue to be interpreted as prohibiting sequential removal from animals of tissues or organs for transplantation.

Transmission of infectious diseases

- 5 The risks associated with possible transmission of infectious diseases as a consequence of xenotransplantation have not been adequately dealt with. It would not be ethical therefore to begin clinical trials of xenotransplantation involving human beings.

- 6 A code of practice should be drawn up specifying which organisms should be excluded from specified-pathogen free animals. Xenotransplantation teams should be required to exclude from source animals all the pathogens listed in the code of practice. A regulatory framework should be devised to control the safety and quality of animal organs and tissue for xenotransplantation.
- 7 Standards and mechanisms for monitoring xenograft recipients and for the action to be taken in case of disease transmission should be in place before human trials begin. It should be a requirement of clinical trials that the need for monitoring is explained to the patient and that it is made clear that consent to the operation also implies consent to subsequent monitoring. Xenotransplantation teams should be required to record all information concerning individual xenograft recipients in a xenotransplantation register maintained by an independent body.
- 8 The Working Party recommends that the Department of Health should establish an Advisory Committee on Xenotransplantation.

Early patients

- 9 No xenotransplantation trials involving human recipients should proceed until the proposed Advisory Committee on Xenotransplantation is in place and has approved the trials. Consent of patients to participation in xenotransplantation trials should be sought by appropriately trained professions who are independent of the xenotransplantation team. The information given to prospective recipients should include an estimation of likely success, attendant risks and subsequent quality of life. No protocol to conduct a trial should be accepted unless it contains a commitment to a robust description and assessment of the patient's pre-operative and post-operative quality of life.
- 10 The first xenotransplantation trials should involve adults rather than children. The first xenotransplantation trials should not involve adults incapable of consenting to participation on their own behalf.
- 11 At any stage in the development of xenotransplantation, patients who, for whatever reasons, refuse xenografts should remain entitled to consideration for human organs on the same basis as before their refusal. Xenograft recipients should remain entitled to consideration for human organ transplantation on the same basis of clinical need as before xenotransplantation.

Effects on the health care system

- 12 If xenotransplantation becomes a treatment of choice, the introduction of the treatment into the NHS should be overseen by the Supra Regional Services Advisory Group.

Personal and social effects of xenotransplantation

- 13 Counselling of xenograft recipients should include discussion of the possible personal impact of xenotransplantation. Research should be initiated to assess the personal impact of xenotransplantation on potential and early recipients.

Implementation of recommendations

14 The Working Party recommends that the proposed Advisory Committee on Xenotransplantation should produce guidance on best practice and revise that guidance in the light of experience. The responsibilities of the Advisory Committee should include:

- assembling and assessing information about the possible risks of disease transmission, and on that basis making recommendations
- establishing a regulatory mechanism to ensure that the appropriate infectious organisms are eliminated from source animals
- developing guidance on the monitoring of future recipients of xenografts and maintaining a register of xenograft recipients
- approving any xenotransplantation trials involving human recipients and the centres that may undertake such trials
- overseeing issues of consent and conscientious objection
- assessing the impact of xenotransplantation on individual recipients
- facilitating debate and assessing attitudes to xenotransplantation.

No xenotransplantation trials involving human recipients should proceed until the proposed Advisory Committee on Xenotransplantation is in place and the above issues have been addressed.